Value of outcomes research in colorectal cancer care

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Chapter 8

LOCALLY ADVANCED COLON CANCER; EVALUATION OF CURRENT CLINICAL PRACTICE AND TREATMENT OUTCOME AT POPULATION LEVEL.

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ABSTRACT

Background: The aim of this study was to evaluate current clinical practice and treatment outcomes regarding locally advanced colon cancer (LACC) at population level.

Patients/Methods: Data from the Dutch Surgical Colorectal Audit (DSCA) from 2009 to 2014 were used. A total of 34,527 patients underwent resection for non-LACC and 6,918 for LACC. The latter was defined as cT4 and/or pT4 stage. LACC was divided into those with multivisceral resection (LACC-MV (n=3,385)) and without (LACC-noMV (n=1,595)). Guideline adherence, treatment strategy, and short term outcomes were evaluated.

Results: Guideline adherence regarding preoperative imaging was more than 90% and 80% regarding preoperative multidisciplinary team discussion. In the elective setting, neoadjuvant (chemo)radiotherapy was applied in 6.2% of the cT4 cases and neoadjuvant chemotherapy in 4.0%. R0 resection rates were 99%, 91% and 87% in non-LACC, LACC-noMV and LACC-MV patients, respectively ($p<0.001$). A postoperative complicated course occurred in 17%, 25% and 29% ($p<0.001$), and the 30 day/in-hospital mortality was 3.6%, 6.0%, and 5.4% ($p<0.001$) in the non-LACC, LACC-noMV and LACC-MV groups, respectively.

Discussion/Conclusion: This population based study suggests that there is room for improvement in the treatment of LACC, with regard to short term surgical outcomes as well as oncological outcomes, i.e. radicality of resection. Improvement might be expected from optimized preoperative imaging, routine MDT discussions, and further specialisation and centralisation of care. Optimized use of neoadjuvant treatment strategies based on already available and upcoming evidence is likely to result in a better margin status and related to that a better long-term prognosis. Furthermore, lower R0 resection rates in emergency setting suggest a potential role for bridging strategies in order to enable optimal staging, neoadjuvant treatment and elective surgery by a surgical team most optimally qualified for the procedure.

BACKGROUND

Colon cancer is highly prevalent world-wide and a major public health problem.[1] A substantial group of patients (10-15%) presents with locally advanced colon cancer (LACC), which has an important impact on the management and prognosis of the disease.The standard curative intent treatment of LACC is a complete resection of the tumor (R0 resection) followed by adjuvant systemic chemotherapy depending on the age and clinical condition of the patient.[2,3]

LACC can be subdivided into T4a stage with serosal ingrowth and T4b stage with ingrowth into nearby tissues or organs (TNM, 7th edition). In order to achieve a R0 resection of the latter tumors, the surgical approach should include a multivisceral resection with or without neoadjuvant down staging.[4,5] Despite the prevalence of LACC and the relatively poor prognosis, treatment of LACC is still an underexposed area in the field of colorectal cancer care when compared to, for example, the extensive literature on locally advanced rectal cancer.

The Dutch Surgical Colorectal Audit (DSCA) has been evaluating and reporting on the quality of care of primary colorectal cancer surgery since 2009.[6,7] The aim of this study was to evaluate current clinical practice regarding short-term outcomes of the treatment of LACC at population level using DSCA data.

METHODS

Dataset

Data were derived from the DSCA, a disease specific national audit. The audit collects information on patient, tumor, treatment characteristics and outcomes and contains data from approximately 97 percent of all patients who underwent a resection for primary colorectal cancer in the Netherlands. Data-entry is obligatory and data are stored in a highly secured online database. All 92 Dutch hospitals participate and appoint a surgeon who is responsible for data-entry. The dataset is cross-checked several times with data registered in the Netherlands Cancer Registry (NCR) to ensure completeness. Detailed information on the validity, collection and methodology of the dataset has been published previously.[6,7]

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients who underwent surgery between January 1st 2009 and December 31st 2014 and were registered before March 15, 2015, were evaluated. Patients with multiple synchronous tumors within the colon were included, but patients with a second tumor in the rectum were excluded. Patients were considered eligible for this study if at least the following data were available: location of the tumor, date of surgery and survival status at the time of hospital discharge. Based on these criteria, 98.7 percent (n=39,491) of all registered patients were available for analysis. Furthermore, for the purpose of the present analysis, all patients with metastatic disease were excluded.

Definitions

In the DSCA, both clinical and pathological T stage were available, but without subdivision in T4a and T4b. LACC was defined as all patients with a registered clinical and/or pathological T4 stage. The extent of surgery for the primary tumor was registered in the DSCA as no, limited or extensive additional resections for local ingrowth. Limited additional resections were defined as resections of the abdominal wall, the omentum or the ovaries. Extensive additional resections referred to resections of the pancreas, spleen, kidney, liver, stomach,

bladder, ureters, uterus or additional bowel resections. The organs involved or the exact locations of the additional resections are not specified. The variable "additional resections for local ingrowth" was used to define two subgroups: LACC without additional/multivisceral resections (LACC-noMV) and LACC with limited or extended additional/multivisceral resections (LACC-MV). All other colon cancer resections were referred to as non-LACC. In short, the following three subgroups were used in this study: LACC-noMV: patients who underwent a resection of a cT4 and/or pT4 colon carcinoma without the need for a multivisceral resection; LACC-MV: patients who underwent a multivisceral resection of a cT4 and/or pT4 colon carcinoma; Non-LACC: patients who underwent a resection for a T1-3 colon cancer (i.e. a tumor that was not classified as either cT4 or pT4).

Emergency surgery was defined as surgery performed within 12 hours after the procedure was scheduled. Urgent surgery referred to semi-urgent procedures that were scheduled more than 12 hours before being performed, but outside of the elective program. Surgical approach was either open, laparoscopic or converted laparoscopic surgery. Hospital volume was defined as the number of resections performed for LACC-MV per hospital per year.

The outcome variables were guideline adherence (see below for the guidelines), radicality of resection and postoperative course. The subcategories for radicality of resections were: R0: complete tumor resection with all margins histologically uninvolved; R1: incomplete resection with microscopic surgical resection margin involvement; R2: incomplete tumor resection with gross residual tumor that was not resected. A complicated course referred to a postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death. Surgical complications were complications directly related to the surgical procedure (i.e. anastomotic leakage, abscess, bleeding, ileus). Non-surgical complications were not directly related to the surgery (i.e. postoperative pneumonia). Mortality was defined as 30 day or in-hospital mortality.

Treatment for LACC according to the Dutch guidelines

The Dutch colorectal guideline used until June 2014 advised to routinely perform a preoperative CT scan for colon cancer. In case

of LACC, this was aimed at optimizing the surgical approach with 'en bloc' multivisceral resection and at considering neoadjuvant therapy. Preoperative (chemo)radiotherapy had to be considered if R0 resection was not found to be achievable based on CT imaging or intraoperative findings from explorative laparotomy. Postoperative (chemo)radiotherapy had to be considered in cases of R2 resection with clipping of the operative field. In the revised guideline of June 2014 (www.oncoline.nl), preoperative imaging as well as multidisciplinary team (MDT) discussion was recommended in order to select the optimal treatment strategy. Preoperative systemic therapy is added as a neoadjuvant treatment option, besides (chemo)radiotherapy. Postoperative (chemo)radiotherapy for LACC is no longer advised.

Statistical analysis

Differences in baseline characteristics and outcome variables between patients with non-LACC, LACC-noMV and LACC-MV were analyzed using a Chi square test or Fisher's exact test in the case of categorical variables. The Kruskal-Wallis one-way analysis of variance was used for continues (nonparametric) variables. R0 resection proportions were compared between different subgroups based on the type of resection, surgical approach, neo-adjuvant treatment and hospital volume. To determine potential improvement in quality of care over time, outcome parameters were plotted against year of registration. The trend over time was analyzed using the Chi square for linearity. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed in PASW Statistics, version 22 (SPSS inc., Chicago, IL).

RESULTS

Patients

Of all colon cancer patients registered between the 1st of January 2009 and the 31st of December 2014 in 92 Dutch hospitals, 39,491 were eligible for analysis. A total of 4,964 patients were staged as M1 and excluded from this analysis. Clinical T stage was known in only 27% of the remaining 34,527 patients and cT4 stage was registered in 578 patients. A total of 4730 patients had a pathological T4 tumor. There

was an overlap between these two groups in the case of 328 patients who had both a cT4 and pT4 classified tumor. This resulted in a total of 4,980 patients with a cT4 and/or pT4 stage (LACC) and the remaining 29,547 (86%) were non-LACC patients (figure 1). In the LACC group, 3,385 patients (68%) were classified as LACC-noMV and 1,595 patients (32%) as LACC-MV. Limited and extensive additional resections were performed in 53% and 47% of the LACC-MV patients, respectively.

Baseline characteristics and surgery

Baseline characteristics of the three subgroups are outlined in table 1. Compared to non-LACC patients, patients with LACC-noMV as well as those with LACC-MV experienced more preoperative tumor complications (34% vs. 51% and 52% respectively). The percentage of procedures in emergency/urgent setting was 14% for non-LACC and 33% and 29% for LACC-noMV and LACC-MV patients, respectively. LACC was associated with a higher proportion of nodal positivity compared to non-LACC. Within the LACC group, nodal positivity was higher for LACC-noMV compared to LACC-MV (60% vs. 47%).

The surgical procedure commenced laparoscopically in 53% of patients with non-LACC, in 36% of those with LACC-noMV and in 21% of those with LACC-MV. Conversion rates were 13%, 19% and 52%, respectively. The proportion of primary anastomoses was considerably lower in LACC-MV patients compared to LACC-noMV and non-LACC patients (table 1).

Guideline adherence

Preoperatively, a CT-abdomen at the least was performed in 92% of patients with LACC-noMV and in 95% of the patients with LACC-MV (table 2). These percentages were slightly higher (94% and 96%, respectively) if emergency/urgent procedures are excluded. Patients undergoing elective surgery were discussed during a MDT meeting in 80% and 82% of LACC-noMV and LACC-MV patients, respectively. Considering cT4 stage in the elective setting only, 6.2% (n=22) of patients with LACC (either no-MV or MV) received neoadjuvant (chemo) radiotherapy and 4.0% (n=14) neoadjuvant systemic therapy.

Outcome variables

As compared to non-LACC, the overall R0 resection proportion was lower in LACC patients (99% vs. 90% respectively) (table 3). A higher proportion of R1/R2 resections was found for LACC-MV as compared to LACC-noMV ($p < 0.001$), also in the elective setting only ($p<0.001$). R0 resection proportions were significantly higher in the elective setting as compared to the emergency and urgent settings for both LACC-noMV (93 vs. 87%; $p<0.001$) and LACC-MV (90% vs. 81%; $p<0.001$). In the LACC-noMV group, the R0 resection proportion was significantly lower in converted procedures than in laparoscopically completed resections (89% vs. 96%; $p<0.001$) though similar R0 resection proportions were found in the LACC-MV group (90% after conversion vs. 93% after laparoscopy). The R0 resection proportions following any form of neoadjuvant treatment did not significantly differ from the overall groups.

In table 4, data on the postoperative course are displayed. The length of stay was the longest for the LACC-MV subgroup. Additionally, complications occurred most often in the LACC-MV group. 30 day / in-hospital mortality rate was significantly higher for LACC compared to non-LACC (5.8% vs. 3.6%; $p<0.001$) without significant impact of multivisceral resection ($p=0.606$) in LACC patients (table 4).

Patients with LACC-MV were treated in all 92 hospitals. Based on the number of LACC-MV patients treated, the hospitals were subdivided into low (≤5 procedures annually) and high (>5 procedures annually) volume hospitals. There were 82 low volume hospitals (median volume 2.3; range 0.2-5.0) and 10 high volume hospitals (median volume 6.9; range 5.2-8.2). The R0 resection proportion was 86% in low volume hospitals, as compared to 91% in high volume hospitals ($p=0.024$).

When looking at the development of the quality of surgical care throughout the years, a significantly positive trend in completeness of resection, postoperative complicated course and 30 days / in-hospital mortality could be observed in the non-LACC and LACC-noMV groups in figure 2. These improvements were less clear (and non-significant) in the LACC-MV group (figure 2).

DISCUSSION

This population study reports on clinicopathological characteristics, treatment strategy and short-term outcomes after resection of M0 LACC in 4,980 patients, who comprise 13% of the registered patients who underwent resection for colon cancer during a 6-year study period in the Netherlands. Only a small proportion of LACC patients was treated with neoadjuvant chemo- and/or radiotherapy. The overall R0 resection proportion was 90% in LACC patients, with the lowest proportion being 81% for patients who underwent a multivisceral resection in a non-elective setting. LACC patients had a slightly worse postoperative outcome compared to non-LACC patients. Short-term outcomes improved over time for LACC-noMV with the R0 resection proportion exceeding 95%. For LACC-MV, improvement over time was less clear and the R0 resection proportion in 2014 was 88%.

An R1 resection of a primary colon cancer has a strong and stage independent negative prognostic impact on the survival and recurrence rate.[8] In a recent single institutional cohort study, recurrence rates were 56% and 19% for R1 and R0 resection, respectively, with corresponding 5-year survival rates of 25% and 60%.[9] Similar to our findings, the risk of incomplete resection was related to the T stage. R0 resection proportions were remarkably low: 65% for T4a and 50% for T4b. Another population based study reported a 75% R0 resection proportion in 861 patients with T4a stage colon cancer.[10] These data from literature and our findings suggest that there is room for improvement in LACC surgery. This will have a positive impact on prognosis given its independent association with recurrence and survival. Furthermore, the postoperative mortality for LACC of 5.8% also suggests room for improvement. This mortality rate is comparable to published series on LACC (3.3 – 8.9%)[11–13]. However, this is a population-based study of unselected patients including emergency surgery and non-expert centers. The volume-outcome relationship in the present analysis suggests the potential benefit of further specialization and centralization of care in high volume centers. The small differences in absolute numbers of procedures between ‘low’ and ‘high’ volume hospitals (2.3 vs. 6.9 respectively), as well as the relatively low median volume in the ‘high’ volume group (6.9), show that LACC surgery has not yet been centralized in the Netherlands. Further improvement might

be expected when annual volumes exceed 15 to 20[14]. The low hospital volumes for LACC-MV might also explain the absence of improvement over time for LACC-MV. Furthermore, lower R0 resection proportions in the emergency and urgent settings suggest a potential role for bridging strategies, such as a decompressing stoma. This would enable optimal staging, potential neo-adjuvant treatment and elective surgery by an optimal surgical team.

A multivisceral resection is essential to achieve a R0 resection in pT4b stage colon cancer and has been associated with improved outcome at population level.[15] However, preoperative as well as intraoperative assessment of organ involvement is often inaccurate, because of the difficulty in distinguishing between true tumor invasion and inflammatory adhesions.[16,17] Reported 'true' pT4 rates in multivisceral resections were 55, 36 and 34% in three studies. [12,18,19] Therefore, multivisceral resection often turns out to be overtreatment. This is a clinically relevant problem because of the increased morbidity rates as shown by our results and others.[13,17] Despite its drawbacks, a multivisceral resection seems to be preferred over a less radical approach in clinically adherent tumors with uncertainty regarding the extent of malignant invasion, bearing in mind the negative prognostic impact of an irradical resection.[20–22]

In addition to extensive surgery, neoadjuvant therapies could optimize R0 resection proportions in LACC.[23,24] In contrast to other types of gastrointestinal cancer, administration of neoadjuvant therapy in colon cancer remains uncommon.[10,13,25,26] Incidental use of a variety of neoadjuvant therapy schedules has been described. In the phase-II Foxtrot trial,[5] 150 patients with LACC were randomized (2:1) between an experimental arm with preoperative chemotherapy (FOLFOX) and a second randomization in RAS wild type for an anti-EGFR antibody, and a control arm with routine adjuvant chemotherapy only. Preoperative systemic therapy was shown to reduce tumor size and resulted in a significant improvement of R0 resection proportion (96% vs. 80%). The need for emergency or urgent surgery, complication rate and toxicity were comparable across both groups. These findings were confirmed in another phase II study including 22 patients and the PRODIGE 22-ECKINOXE trial with a similar design is currently recruiting. [27,28] In the present study, neoadjuvant therapy was not associated with a higher percentage of R0 resections. This may be the result of both small sample

size (n=77) and allocation bias, since the most advanced tumors were probably allocated to neoadjuvant therapy.

Due to concerns regarding radiation toxicity, mainly concerning the small bowel, the use of (chemo)radiotherapy for LACC remains controversial.[29] One study, in which 33 patients were retrospectively analyzed, suggested that neoadjuvant (chemo)radiotherapy combined with en bloc multivisceral resection results in high R0 resection proportions and excellent local control, with acceptable morbidity and mortality.[16] In 64% of these patients, the T4 tumor was located in the sigmoid. The sigmoid was also the main tumor location (68%) in patients who received neoadjuvant (chemo) radiotherapy in the present study.

Decisions on neoadjuvant therapy strategies should be based on preoperative imaging, but the accuracy is limited and over staging rates of up to 50% have been described.[12,30] In this study a comparable discrepancy between cT4 and pT4 was found; in 833 of the pT4 patients, clinical T stage was registered with 61% being classified as cT1-3. Only 57% of the 578 cT4 tumors was classified as pT4 tumor. Despite its limited accuracy, preoperative imaging seems to be essential when considering neoadjuvant treatment and surgical planning. Therefore, further improvement can be expected from optimal guideline adherence with respect to preoperative imaging and MDT discussion. LACC is often considered to be a contra indication for laparoscopic surgery, due to oncological concerns. In this series, laparoscopic surgery was performed in 31% of LACC overall and 21% of LACC-MV with conversion rates of up to 52%. Conversion did not lower the R0 resection proportion in LACC-MV patients, which suggests that it can be considered safe to initiate surgery laparoscopically. In contrast, conversion did result in lower R0 resection proportions in the LACC-noMV group. The latter finding is remarkable and was not confirmed in the literature. Several non-randomized comparative studies have been published on laparoscopy in LACC.[10,13,25,26,31,32] The laparoscopic group often had favorable baseline characteristics with regard to factors such as previous abdominal surgery and emergency setting. Additionally, resections were less often multivisceral. Conversion rates ranged between 7% and 24% and R0 resection proportions were mostly similar to the open surgery groups. These data are most likely skewed by allocation bias. Increasing the rate of laparoscopic surgery for LACC might contribute to a lower morbidity rate, but this may never jeopardize oncological safety.

This is a large population based cohort study, which provides the best available evidence of the nationwide current clinical practice regarding LACC. However, several limitations of this design should be kept in mind. The availability of data is dependent on the self-reported data from the DSCA database, which is subject to registration bias and incomplete data registration. Nonetheless, data were validated on a yearly basis using the Dutch National Cancer Registry, in order to show accuracy and completeness of data[6]. Also, the variable set is chosen for the purpose of clinical auditing and several variables relevant to the aim of this study such as subdivision in T4a/b subgroups and organ involvement based on pathology reports are lacking. Additionally, the clinical T stage was unknown in a substantial number of patients, resulting in a small sample size of clinical T4 tumors, which is the relevant group to assess for neoadjuvant strategies. Furthermore, differences in patient and tumor characteristics between subgroups should be recognized when comparing outcome variables between the relevant subgroups.

In conclusion, amongst patients who undergo surgery for LACC there is a lower R0 resection proportion and they are at higher risk of postoperative complications and mortality as compared to patients who receive surgery for less invasive colon cancer. Neoadjuvant therapy for colon cancer is still rarely applied in the Netherlands and prospective randomized studies have to be awaited in order to confirm the observation of more radical resections in phase 2 studies. Considering the relatively low R0 resection proportion, there is an opportunity for improvement. This may be achieved by optimizing preoperative imaging, the application of neoadjuvant therapy schedules and centralization and specialization.

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TABLES AND FIGURES

Table 1. Baseline characteristics. LACC: Locally advanced colon cancer, MV: multivisceral resection required.

		non-LACC		LACC- noMV		LACC-MV		
		n	%	*n*	%	*n*	%	χ^2
Sex	Male	15502	52	1669	49	708	44	<0.001
	Female	14044	48	1716	51	886	56	
Age	≤ 60	4600	16	526	15	259	16	0.005
	61-70	8405	28	939	28	462	29	
	71-80	10520	36	1140	34	527	33	
	≥ 81	6014	20	780	23	347	22	
ASA score	I - II	21866	75	2357	71	1146	72	<0.001
	III	6844	23	886	27	408	26	
	IV - V	534	1.8	98	2.9	36	2.3	
Preoperative complications caused by the tumor	None	19470	66	1658	49	759	48	<0.001
	Perforation with faecal peritonitis	334	1.1	180	5.4	69	4.4	
	Abscess	214	0.7	90	2.7	94	5.9	
	Obstruction	3236	11	805	24	324	21	
	Blood loss / anaemia	4649	16	419	13	176	11	
	Other	1416	4.8	209	6.2	162	10	

Continuation of Table 1

Operative setting	Elective (incl. following stent placement)	25349	86	2250	67	1125	71	<0.001
	Emergency / urgent	4151	14	1132	33	470	29	
Pathologic N-stage	N0	19328	66	1336	40	847	54	<0.001
	N1	6733	23	1081	33	436	28	
	N2	3035	10	907	27	294	19	
	Nx	325	1.1	44	1.3	15	0.9	
Surgical approach	Open	13999	47	2175	64	1247	78	<0.001
	Laparoscopic	13587	46	982	29	166	10	
	Laparoscopic – converted	1961	6.6	228	6.7	182	11	
Surgical procedure	Ileocecal resection	325	1.1	61	1.8	21	1.3	<0.001
	(Extended) right hemicolectomy	13316	45	1679	50	677	42	
	Transverse resection	774	2.6	79	2.3	75	4.7	
	(Extended) left hemicolectomy	3186	11	383	11	215	14	
	(Low) anterior / sigmoid resection	10970	37	1038	31	548	34	
	Subtotal colectomy	545	1.8	77	2.3	37	2.3	
	Panproctocolectomy	174	0.6	10	0.3	5	0.3	
	Other	257	0.9	58	1.7	17	1.1	
Anastomosis	Anastomosis	25562	88	2611	79	1131	73	<0.001
	Anastomosis with diverting ostomy	1076	3.7	144	4.3	123	7.9	
	End ostomy	2352	8.1	567	17	300	19	

Table 2. Guideline adherence. LACC: Locally advanced colon cancer, MDT: multidisciplinary team discussion, MV: multivisceral resection required. *In the DSCA database, preoperative imaging is registered for the abdomen and thorax separately. The imaging modality is further specified for both compartments, and only the one with highest accuracy is registered in case of multiple modalities. **Analysed as fulfilling guideline recommendation for preoperative imaging.

				LACC-noMV		LACC-MV	
				n	%	n	%
Elective, emergency and urgent procedures	**Preoperative imaging***	**Abdomen**	**none**	93	2.8	18	1.2
			ultrasound	184	5.6	61	3.9
			CT	2912	89	1406	91
			MRI-liver**	31	0.9	15	1.0
			PET-CT**	63	1.9	47	3.0
		Thorax	**none**	305	9.1	86	5.5
			X-thorax	2292	68	1062	68
			CT	694	21	373	24
			PET-CT**	65	1.9	47	3.0
Elective procedures only	**Preoperative imaging***	**Abdomen**	**none**	18	0.8	3	0.3
			ultrasound	128	5.8	44	4.0
			CT	1982	90	993	91
			MRI-liver**	26	1.2	11	1.0
			PET-CT**	57	2.6	40	3.7
		Thorax	**none**	79	3.5	30	2.7

Continuation of Table 2

		X-thorax	1561	70	740	67
		CT	538	24	294	27
		PET-CT*	58	2.6	39	3.5
	MDT		1784	80	919	82
Elective procedures cT4	**Neoadjuvant therapies**	**chemotherapy**	2	1.1	12	6.7
		(chemo)radiotherapy	5	2.9	17	9.5

Table 3. Radicality of resection. CT: chemotherapy; (C)RT: (chemo)radiotherapy; LACC: locally advanced colon cancer, MV: multivisceral resection required, R0: complete tumor resection with all margins histologically uninvolved, R1: incomplete resection with microscopic surgical resection margin involvement, R2: incomplete tumor resection with gross residual tumor that was not resected.*Only elective procedures included. ** Analysed using Fisher's exact test.

		non-LACC		LACC-noMV		LACC-MV		
		n	%	*n*	%	*n*	%	χ^2
Overall	R0	28605	99	2981	91	1363	87	<0.001
	R1	222	0.8	190	5.8	135	8.7	
	R2	51	0.2	93	2.8	62	4.0	
Elective procedures	R0	24618	99	2040	93	990	90	<0.001
	R1	146	0.6	95	4.3	79	7.2	
	R2	32	0.1	50	2.3	29	2.6	
Emergency/urgent	R0	3949	98	938	87	373	81	<0.001
procedures	R1	72	1.8	95	8.8	56	12	
	R2	18	0.4	43	4.0	33	7.1	
Open	R0	13453	99	1855	89	1049	86	<0.001
	R1	132	1.0	142	6.8	111	9.1	
	R2	32	0.2	78	3.8	57	4.7	
Laparoscopic	R0	13257	99	926	96	153	93	<0.001
	R1	65	0.5	31	3.2	10	6.1	
	R2	12	0.1	7	0.7	1	0.6	

Continuation of Table 3

Laparoscopic - converted	R0	1895	98	200	89	161	90	<0.001
	R1	25	1.3	17	7.6	14	7.8	
	R2	7	0.4	8	3.6	4	2.2	
Neoadjuvant CT*	R0			22	85	47	92	0.429**
	R1			2	7.7	3	5.9	
	R2			2	7.7	1	2.0	
Neoadjuvant (C)RT*	R0			9	90	40	83	0.321**
	R1			0	0.0	6	13	
	R2			1	10	2	4.2	

Table 4. Postoperative course and complications. LACC: locally advanced colon cancer, MV: multivisceral resection required. Complicated course: postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death. Mortality: 30-day / in-hospital mortality. *Median (IQR); **Analysed using Kruskal-Wallis one-way analysis of variance.

	non-LACC		**LACC-noMV**		**LACC-MV**		
	n	***%***	***n***	***%***	***n***	***%***	χ^2
Length of stay (days)	7 (5-11)*		8 (5-14)*		10 (7-16)*		<0.001**
Complicated course	5509	17	837	25	460	29	<0.001
Non-surgical complications	3859	13	561	17	254	16	<0.001
Surgical complications	3698	13	494	15	290	18	<0.001
Surgical re-intervention	2816	9.5	355	11	185	12	0.007
Radiological re-intervention	270	0.9	47	1.4	40	2.5	<0.001
Mortality	1070	3.6	201	6.0	86	5.4	<0.001

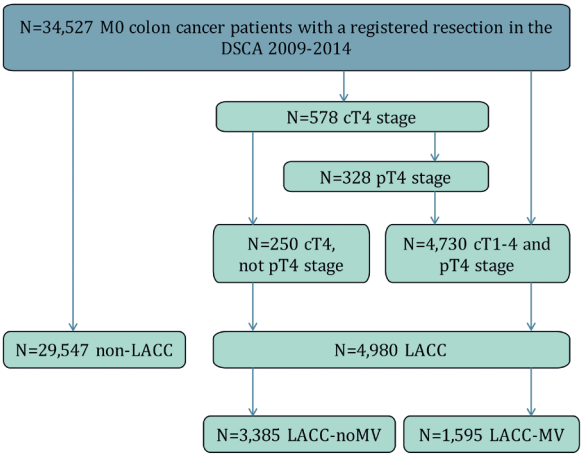

Figure 1. Subdivision of patients into non-LACC, LACC-noMV and LACC-MV. LACC: locally advanced colon cancer, MV: multivisceral resection required.

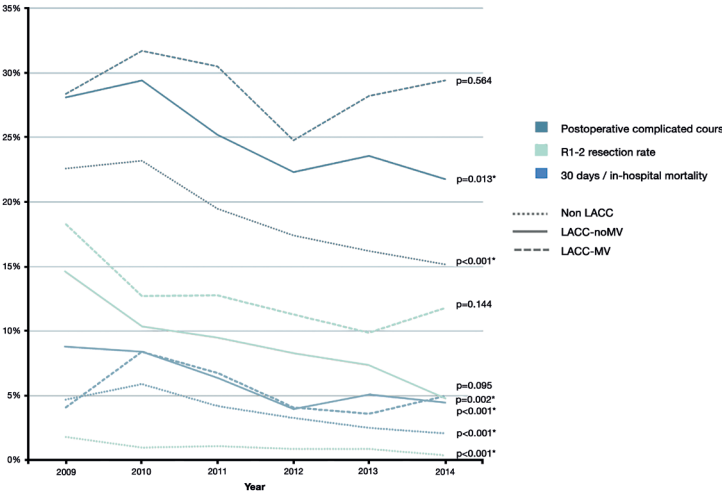

Figure 2. The development of the quality of surgical care for LACC throughout the years. LACC: locally advanced colon cancer, MV: multivisceral resection required. R1: incomplete resection with microscopic surgical resection margin involvement, R2: incomplete tumor resection with gross residual tumor that was not resected. Postoperative complicated course: postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death.